Volumetrics of Brain Development

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Introduction

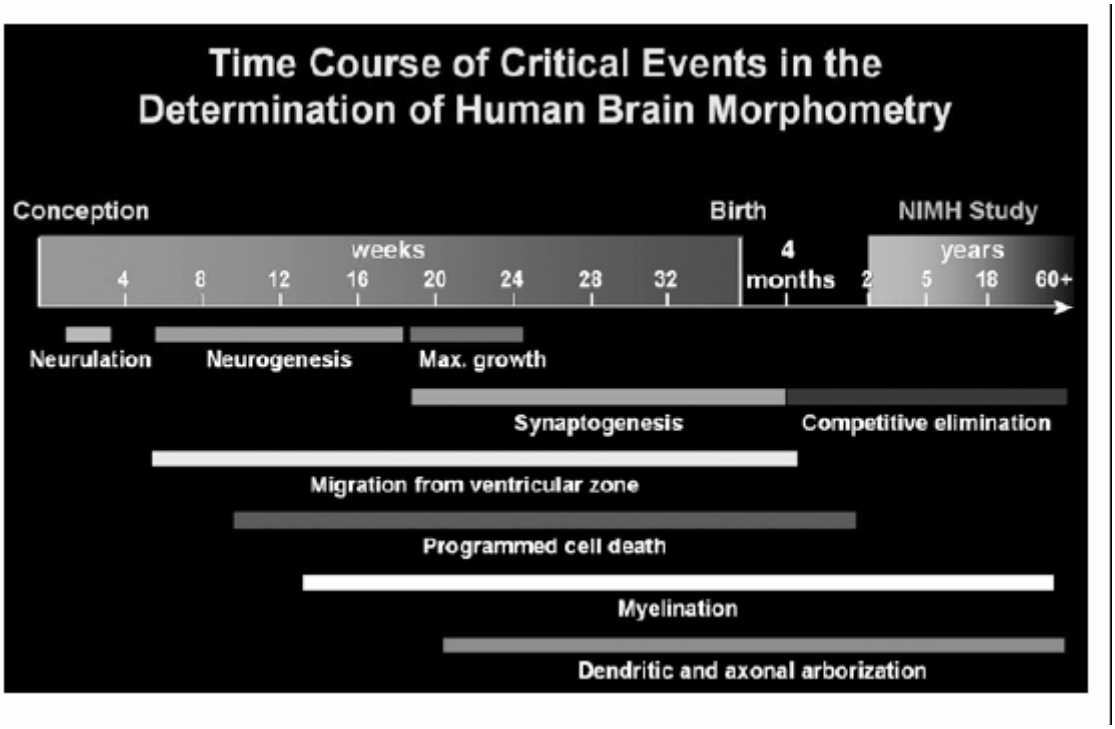
MRI has been particularly important in the study of neurodevelopment because it does not involve exposure to radiation. Therefore it has become accepted as safe for use in children, including healthy children, and for multiple scans during longitudinal studies. This presentation will provide begin with a brief overview of key neurodevelopmental events as a context, then discuss methodological issues unique to pediatric neuroimaging. Results of volumetric imaging studies will be reviewed followed by a discussion of implications for volumetric studies in developing populations.

The development of the nervous system occurs through the interaction of several synchronized processes, some of which are complete before birth, while others continue into adulthood. The first key event in the development of the central nervous system is the formation of a specialized fold of ectodermal tissue called the neural tube. The neural tube nears completion by 3 to 4 weeks of gestation and is the basis for all further nervous system development. From 4 to 12 weeks the neural tube differentiates into what will become various components of the nervous system. From 12 weeks to 20 weeks these neurons multiply and migrate from their origins to destinations in the cortex, moving along a scaffolding of glial cells [1]. After this migration, a period of rapid cell death occurs, reducing the neural number by half from 24 weeks of gestation to 4 weeks after birth. The cell bodies of the neurons, together with other cells called glia, form the gray matter of the brain. Their myelinated axons form white matter.

Myelination occurs regionally beginning with the brain stem at 29 weeks [2] and generally proceeding from inferior to superior and posterior to anterior. Proximal pathways tend to myelinate before distal, sensory before motor, and projection before association[3]. Although most major tracts are significantly myelinated by early childhood, axons within the cortex and in some regions such as the arcuate fasciculus, a white matter bundle near the temporal lobe continue to myelinate into the second and third decades of life[4].

A third major developmental process is the proliferation and organization of synapses, which begins slightly later, around the 20^{th} week of gestation. Synaptic density increases rapidly after birth, reaching by 2 years of age a level approximately 50% greater than that typically seen in adults [5]. This is followed by a regionally specific loss of synaptic connections. For example, maximum synaptic density occurs in the visual cortex at 4 months postnatally, but it does not typically peak in the prefrontal cortex until 4 years of age. Beginning at approximately 15 weeks the surface of the growing brain begins to fold into sulci and gyri[6]. The major sulci, except for the occipital lobe, are in place by 28 weeks of gestation, after which secondary and tertiary sulci are elaborated, with nearly all gyri present by birth. The sulcal and gyral patterns continue to increase in complexity after birth, likely related to changes in cell-packing density and maturation of subcortical tracts.

The dynamic interplay between progressive and regressive events results in relatively rapid brain growth in the first 2 years of life, by which time it has achieved 80% of its adult weight. By age 5 years brain size is approximately 90% of adult size [7]. However, significant remodeling of gray and white matter continues into the third decade of life, something that could not be fully appreciated until the MRI studies described below.



Methodological Issues in Pediatric Neuroimaging

The basics of MRI imaging are being reviewed in a different presentation. Here we will focus on some methodological issues unique to pediatric neuroimaging. Imaging children presents three major challenges relatively unique to pediatric imaging: smaller head size, differing tissue contrast parameters related to changes in myelin and water concentration, and motion. Smaller head size may require specialized equipment to minimize distance between the head coil and the child's brain. In addition smaller sizes may lead to use of higher resolution scans, which will decrease signal to noise ratios unless compensated by longer scanning time. However, another hurdle in imaging particularly very young children is motion artifact. While some clinical populations are sedated for scans, this is not feasible for normative studies. Experienced teams can have success in getting very young children to stay still, most often by encouraging them to fall asleep. Some centers use mock scanners to decrease anxiety, and others use specific training techniques. Nonetheless, motion tends to be more of a problem with younger populations, and limits length of exam times.

These issues also complicate image analysis. Increased noise in images due to higher resolution or motion may affect analysis results. Many image analysis programs currently rely on use of standardized maps against which images are warped into order to improve segmentation routines or provide anatomical labels for specific areas. Warping

pediatric brains against adult templates may introduce artifacts due to age-related differences in size or shape of structures, particularly below age 7[8]. Segmentation of images into different tissue classes is challenging in young children where image contrast has not reached its mature form and in which substantial amounts of white matter have not yet been myelinated. Unique approaches may be necessary, such as defining a fourth tissue class corresponding to nonmyelinated white matter[9]. Older children tend to have less CSF than adults, which can also create problems for some automated methods.

Results of Imaging Studies of Brain Development

The first MRI studies of brain development were reported in the 1980s and focused on qualitative descriptions of gray and white matter during the first 2 years of life [10-14]. With conventional MRI sequences the gray and white matter intensities during the first 6 months are reversed from the adult pattern (i.e. gray matter appears lighter than white matter). From ages 6 to 12 months there is a gradual and regionally specific transition to the adult pattern during which gray and white matter are not well differentiated. Myelination appears similar to adult pattern by 12 months on T1-weighted images and by 24 months on T2-weighted images[10]. The findings are consistent with a decrease in water content in both white and gray matter and the addition of macromolecular precursors to myelination and then myelination itself [2, 15].

MRI studies of brain structure in typically developing children and adolescents were first reported in the 1990s. These confirmed the earlier postmortem findings that total brain volume was approximately 90% of adult size by age 5. White matter volume was generally found to be increasing and gray matter volume decreasing [16-18]. These earlier studies provided seminal insights into anatomic brain development but were cross-sectional and underpowered to detect the more complicated developmental trajectories later confirmed by longitudinal studies.

NIMH Longitudinal Brain Imaging Study

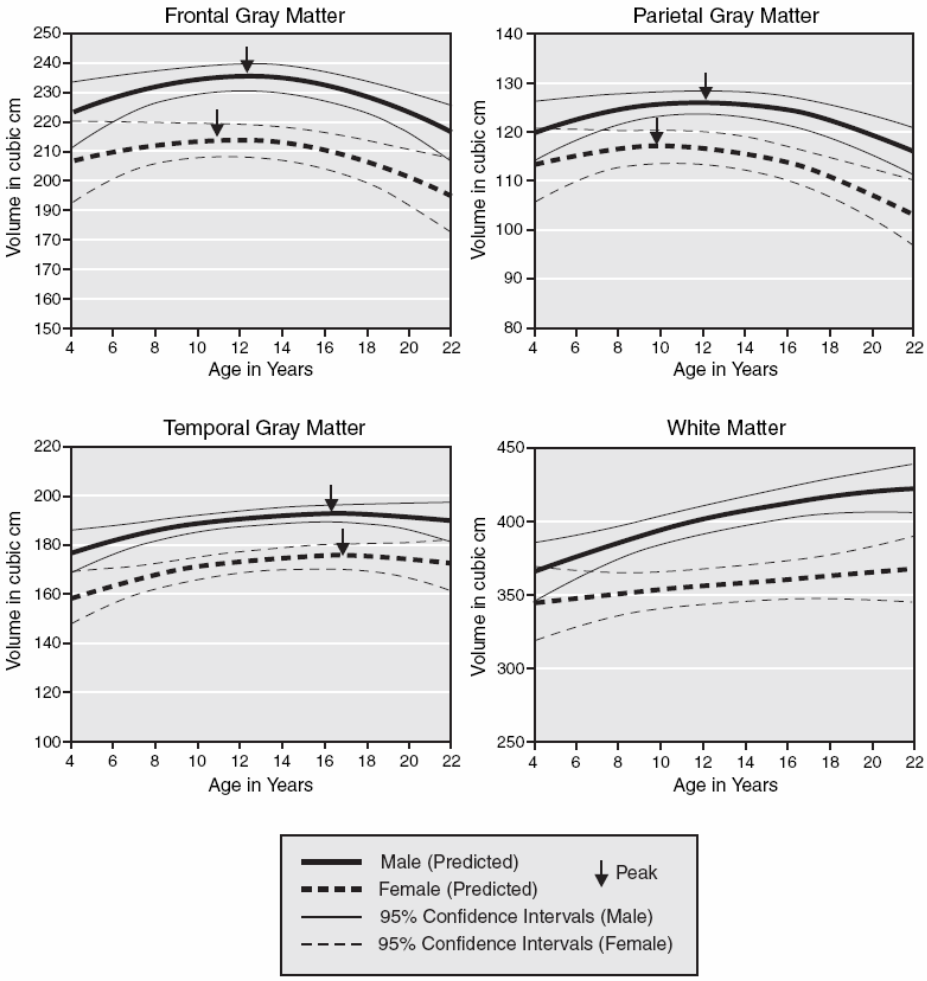
In 1989, the Child Psychiatry Branch at the National Institute of Mental Health (NIMH) initiated the first large scale longitudinal study of normal and abnormal brain development. Initial cross-sectional data indicated that large sample sizes or a longitudinal study design would be required to characterize the developmental changes of the pediatric population[19]. As of December 2005 the data set included approximately 4,000 scans from 2,000 subjects, about half typically developing and half from various diagnostic groups, such as ADHD and childhood-onset Schizophrenia. Healthy control subjects are recruited from the community and undergo physical and neurological exams, clinical interviews, family history assessment, and an extensive neuropsychological battery[20, 21]. Approximately 400 of the subjects are twins. Participants are asked to return for follow-up longitudinal testing and scans at approximately 2 year intervals.

Total cerebral volume peaks at 14.5 years in males and 11.5 years in females [22]. By age 6 years the brain is at approximately 95% of this peak, consistent with earlier postmortem reports. Male brains are approximately 9% larger on average than those of females. This difference is statistically significant, even when controlling for height and weight.

Lateral ventricular volume increases across this age span, a fact not widely appreciated for children and adolescents. The naturally occurring enlargement of

ventricles should be considered in interpreting the reports of increased ventricular volumes, or ventricular-to-brain ratios, reported for several neuropsychiatric conditions. Lateral ventricle volumes, perhaps because they share a border with multiple other structures, tend to have the highest variability of brain morphometric measures.

Cortical gray matter volume tends to follow an "inverted U" developmental course with volumes peaking at different times in different lobes. For instance, frontal lobe gray matter reaches its maximal volume at 11.0 years in girls and 12.1 years in boys; temporal lobe cortical gray matter peaks at 16.7 years in girls and 16.2 years in boys; and parietal lobe cortical gray matter peaks at 10.2 years in girls and 11.8 years in boys [22].



The **basal ganglia** consist of the caudate, putamen, globus pallidus, subthalamic nucleus, and substantia nigra. The basal ganglia have long been known to play a role in the control of movement and muscle tone but more recently have been shown to be involved in circuits mediating higher cognitive functions, attention, and affective states. Our group measured caudate nucleus volumes and found that like the cortical gray matter structures the caudate nucleus follows an inverted U shape developmental trajectory. Caudate size peaks at age 7.5 years in girls and 10.0 years in boys

The **temporal lobes, amygdala, and hippocampus** subserve emotion, language, and memory functions that change markedly between the ages of 4 and 18 years [23-25].

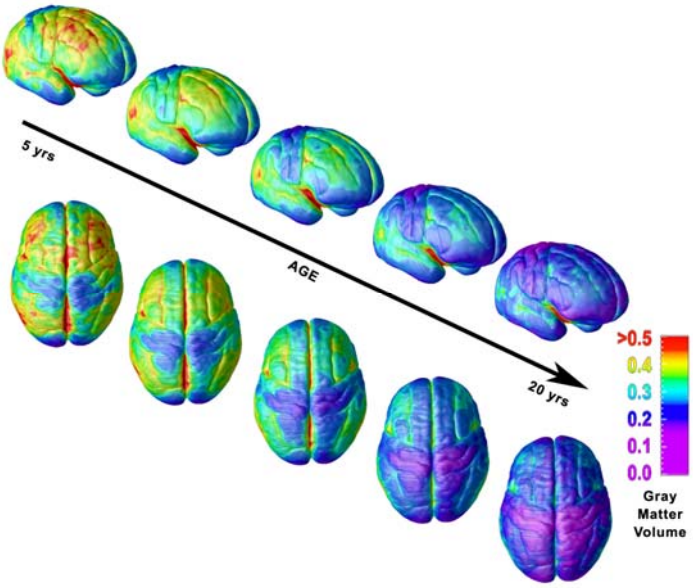
Quantification of the longitudinal data is underway. In a previous cross-sectional study of a subset of this longitudinal data, amygdala volume increased with age significantly only in males and hippocampal volume increased significantly with age only in females [26]. This pattern of gender-specific maturational volumetric changes is consistent with nonhuman primate studies indicating a relatively high number of androgen receptors in the amygdala [27] and a relatively higher number of estrogen receptors in the hippocampus [28], although direct links between receptor density and growth patterns have not been established.

In contrast to the inverted U shape of gray matter developmental curves, the amount of **white matter** in the brain generally increases throughout childhood and adolescence. Although the rate of white matter increase varies with age, we have not detected periods of overall white matter reduction for any region within the age range we have examined [21]. Reports from other groups studying white matter changes in older populations have found that white matter does not begin to decrease until the fourth decade[29]. Unlike the lobar differences seen in gray matter GM trajectories, the white matter slopes are similar in frontal, temporal, and parietal lobes.

The most prominent white matter structure is the **corpus callosum** (CC), consisting of approximately 200 million myelinated fibers, most of which connect homologous areas of the left and right cortex. Several studies have indicated that CC development continues to progress throughout adolescence [30-33] [34], raising the question of whether this may be related to the improvement in these cognitive capacities seen during childhood and adolescence. Effects of sex have been widely debated with some authors finding gender-related differences [31, 35-37]while many have not [38-44]. In the NIMH sample total midsagittal corpus callosum area increased robustly from ages 4 to 18 years, but there were no significant gender effects.

Other measures of developmental changes in brain structures

Description of basic changes in brain volumes with development has been an essential step; however it is recognized that this is a relatively gross measure. In order to explore more precise aspects of brain development many groups have been exploring alternative ways of looking at brain structures, many made newly possible by ongoing improvements in computational and statistical techniques. Several groups are now describing changes in cortical thickness with techniques allowing a voxel-wise level of resolution[45-48]. For example, using the NIMH dataset described above, in collaboration with UCLA we analyzed a group of 13 subjects scanned 4 times at approximately 2 year intervals (see figure below)[49]. The developmental trajectory of cortical gray matter followed a regionally specific pattern with areas subserving primary functions, such as motor and sensory systems, maturing earliest and higher order association areas, which integrate those primary functions, maturing later. The changes over time can be viewed as time-lapse movies (http://www.loni.ucla.edu/~thompson/DEVEL/dynamic.html). Other measures being explored include shape, such as of the corpus callosum,[50, 51] and hippocampus [52]and indexes of gyral and sulcal morphology[53, 54].



Conclusion

The field of pediatric structural neuroimaging has been growing rapidly in response to the realization of the complexity and potential malleability of postnatal brain development. There are now large scale studies underway in several countries combining data from multiple sites in order to increase sample sizes and move towards the compilation of population-based measures of brain development. Advances in scanner technology are making it possible to obtain very high resolution structural data within time frames feasible for pediatric populations. The results seen thus far show that brain volumes are highly variable within populations and show complex changes with development that continue into at least the third decade of life. This underlines the need for longitudinal studies and attention to measuring trajectories in studies of development and the factors that may impact it.

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